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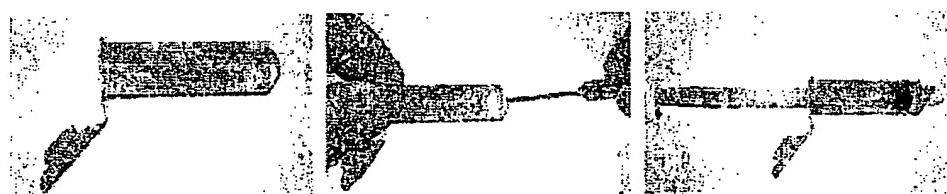
- with international search report
- before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments

(88) Date of publication of the international search report:

30 March 2006

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: GEL-BASED DELIVERY OF RECOMBINANT ADENO-ASSOCIATED VIRUS VECTORS



A

B

C

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(57) Abstract: Disclosed are water-soluble gel-based compositions for the delivery of recombinant adeno-associated virus (rAAV) vectors that express nucleic acid segments encoding therapeutic constructs including peptides, polypeptides, ribozymes, and catalytic RNA molecules, to selected cells and tissues of vertebrate animals. Also disclosed are gel-based rAAV compositions useful in the treatment of mammalian, and in particular, human diseases, including for example, cardiac disease or dysfunction, and musculoskeletal disorders and congenital myopathies, including, for example, muscular dystrophy, acid maltase deficiency (Pompe's disease), and the like. In illustrative embodiments, the invention provides rAAV vectors comprised within a biocompatible gel composition for enhanced viral delivery/transfection to mammalian tissues, and in particular to vertebrate muscle tissues such as a human heart or diaphragm tissue.

INTERNATIONAL SEARCH REPORT

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A. CLASSIFICATION OF SUBJECT MATTER

A61K48/00 A61K47/10 A61K47/14 A61K47/42

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, BIOSIS, EMBASE, PAJ, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category * | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|------------|--|-----------------------|
| X | FRAITES T J ET AL.: "Gel-Based Delivery of Recombinant AAV Vectors to Adult Murine Diaphragm", MOLECULAR THERAPY, vol. 7, no. 5, May 2003 (2003-05), pages S99-S100, XP002349630 USA abstract —/— | 1-47 |

 Further documents are listed in the continuation of box C. Patent family members are listed in annex.

* Special categories of cited documents :

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the international filing date
- *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the international filing date but later than the priority date claimed

- *T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- *X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- *Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
- *8* document member of the same patent family

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| C(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT | | |
|---|--|-----------------------|
| Category * | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
| P,X | <p>MAH CATHRYN ET AL: "A new method for recombinant adeno-associated virus vector delivery to murine diaphragm." MOLECULAR THERAPY : THE JOURNAL OF THE AMERICAN SOCIETY OF GENE THERAPY. MAR 2004, vol. 9, no. 3, 10 February 2004 (2004-02-10), pages 458-463, XP002349631 ISSN: 1525-0016 cited in the application the whole document</p> <p>-----</p> | 1-47 |
| X | <p>US 6 333 194 B1 (LEVY ROBERT J ET AL) 25 December 2001 (2001-12-25)</p> <p>column 1 column 3, line 33 - line 53 column 4, line 13 - line 36 column 4, line 64 - column 5, line 8 column 7, line 12 - line 15 column 7, line 46 - line 54 column 9, line 1 - line 36 column 13, line 10 - line 11 column 15, line 63 - column 17, line 16 column 29, line 8 - line 11 column 30, line 16 - line 25 column 35, line 6 - line 59 examples 1,8</p> <p>-----</p> | 1-47 |
| X | <p>EP 0 844 004 A (KOKEN COMPANY LIMITED; SUMITOMO PHARMACEUTICALS COMPANY, LIMITED) 27 May 1998 (1998-05-27)</p> <p>column 2, line 25 - column 3, line 15 column 3, line 55 - line 58 examples 1,2,4,8,TE2</p> <p>-----</p> | 1-47 |
| X | <p>WO 00/50584 A (UNIVERSITY OF IOWA RESEARCH FOUNDATION) 31 August 2000 (2000-08-31)</p> <p>page 14, line 29 - page 15, line 11 page 16, line 21 - page 17, line 2 page 31, line 10 claims 3,38</p> <p>-----</p> | 1-47 |
| A | <p>SIEMENS D R ET AL: "VIRAL DELIVERY IN A GELATIN SPONGE MATRIX ENHANCES GENE EXPRESSION AND ANTITUMOR ACTIVITY IN A MURINE PROSTATE CANCER MODEL" JOURNAL OF UROLOGY, BALTIMORE, MD, US, vol. 161, no. 4 SUPPL, 2 May 1999 (1999-05-02), page 61, XP000939393 ISSN: 0022-5347 abstract</p> <p>-----</p> <p>-/-</p> | 1-47 |

INTERNATIONAL SEARCH REPORT

PCT/US2005/004146

| C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT | | |
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| Category * | Character of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
| A | FRAITES THOMAS J JR ET AL: "Correction of the enzymatic and functional deficits in a model of Pompe disease using adeno-associated virus vectors." MOLECULAR THERAPY : THE JOURNAL OF THE AMERICAN SOCIETY OF GENE THERAPY. MAY 2002, vol. 5, no. 5 Pt 1, May 2002 (2002-05), pages 571-578, XP002349632 ISSN: 1525-0016 cited in the application the whole document | 1-47 |
| A | FRAITES THOMAS J ET AL: "Gene replacement therapy for glycogen storage disease type II with recombinant adeno-associated virus serotype 1 (AAV1) vectors." CIRCULATION, vol. 106, no. 19 Supplement, 5 November 2002 (2002-11-05), pages II-127, XP009055572 & ABSTRACTS FROM SCIENTIFIC SESSIONS; CHICAGO, IL, USA; NOVEMBER 17-20, 2002 ISSN: 0009-7322 the whole document | 1-47 |
| A | MAH C ET AL: "Improved method of recombinant AAV2 delivery for systemic targeted gene therapy" MOLECULAR THERAPY, ACADEMIC PRESS, SAN DIEGO, CA., US, vol. 6, no. 1, July 2002 (2002-07), pages 106-112, XP002967965 ISSN: 1525-0016 cited in the application the whole document | 1-47 |
| A | TRUONG-LE V L ET AL: "DELIVERY OF DNA VACCINE USING GELATIN-DNA NANOSPHERES" PROCEEDINGS OF THE 24TH. INTERNATIONAL SYMPOSIUM ON CONTROLLED RELEASE OF BIOACTIVE MATERIALS. STOCKHOLM, JUNE 15 - 19, 1997, PROCEEDINGS OF THE INTERNATIONAL SYMPOSIUM ON CONTROLLED RELEASE OF BIOACTIVE MATERIALS, DEERFIELD, IL., CONTROLLED RELEASE, vol. SYMP. 24, 1997, pages 39-40, XP000828044 ISSN: 1022-0178 the whole document | 1-47 |
| | | -/- |

INTERNATIONAL SEARCH REPORT

PCT/US2005/004146

| C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT | | |
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| Category * | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
| A | DAI QUAN ET AL: "Adenovirus-mediated gene transfer to healing tendon: Enhanced efficiency using a gelatin sponge." JOURNAL OF ORTHOPAEDIC RESEARCH, vol. 21, no. 4, July 2003 (2003-07), pages 604-609, XP002349633 ISSN: 0736-0266 the whole document | 1-47 |

INTERNATIONAL SEARCH REPORT

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Box II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. Claims Nos.: because they relate to subject matter not required to be searched by this Authority, namely:
Although claims 32-47 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. Claims Nos.: because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. Claims Nos.: because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1. As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

46 (entirely); 1-45, 47 (partially)**Remark on Protest**

- The additional search fees were accompanied by the applicant's protest.
 No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. claims: 46 (entirely); 1-45,47 (partially)

Pharmaceutical use of a gel-formulation of adeno-associated viral vector comprising acid alpha-glucosidase (Gaa) for the treatment of Pompe disease.

2. claims: 1-45,47 (partially)

Pharmaceutical use of a gel-formulation of adeno-associated viral vector comprising dystrophin for the treatment of Duchenne muscular dystrophy.

3. claims: 1-45,47 (partially)

Pharmaceutical use of a gel-formulation of adeno-associated viral vector comprising alpha-1 antitrypsin for the treatment of a muscular myopathy / dystrophy.

INTERNATIONAL SEARCH REPORT

Information on patent family members

PCT/US2005/004146

| Patent document cited in search report | Publication date | Patent family member(s) | | Publication date |
|--|------------------|-------------------------|---|--|
| US 6333194 | B1 | 25-12-2001 | NONE | |
| EP 0844004 | A | 27-05-1998 | AU 704694 B2 AU -6243696 A CA 2225998 A1 CN 1193916 A WO 9702047 A1 NZ 311175 A TW 577747 B | 29-04-1999 05-02-1997 23-01-1997 23-09-1998 23-01-1997 29-11-1999 01-03-2004 |
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